SDD

Benus, R. F.; Harmsen, H. J.; van der Werf, T. S.

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R. F. Benus
H. J. Harmsen
T. S. van der Werf

SDD: don't be selective in considering pros and cons

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Dear Editor,

We thank Dr. Zandstra and colleagues [1] for their interest in our work [2]. Although in their scientific careers they have amassed impressive data on selective digestive microbial decontamination (SDD), they have not fully appreciated what our paper adds to this large body of knowledge.

The intestinal microbiota contains many more cells than the human body itself. Furthermore the intestinal microbial gene set is approximately 150 times larger than the human genome [3]. Last year marked the 150th anniversary of Darwin's *On the Origin of Species*. How can we explain any genetic advantage for humans to carry so many microbes along? What benefit does our microbiome provide us during health? And what happens during critical illness? How does the intensive care unit (ICU) environment impact on our microbiota? What impact does SDD have on our microbiota? And what is the impact of SDD on the emergence of resistant bacteria in the ICU?

Zandstra et al. rightly allude to the fact that *Enterobacteriaceae* increase during critical illness—we also found a more than tenfold relative increase (as a percentage of total bacteria) compared to data from healthy volunteers [4, 5]. To fight overgrowth of *Enterobacteriaceae* seems like a good idea—but is there a trade-off? Why did SDD—though providing a small but significant survival advantage compared to a control group—fail to further reduce mortality compared with patients receiving only oral topical antimicrobial products, even though these study participants had similarly increased percentages of *Enterobacteriaceae*?

A potential advantage of having such massive numbers of anaerobic bacteria in the colon is that colonocytes feed on bacterial products. Indeed colonocytes feed on butyrate, produced by a limited number of colonic bacterial species. The *Faecalibacterium prausnitzii* group is predominant amongst these butyrate-producing groups. This group is already reduced during tube feeding, resulting in a significantly reduced concentration of butyrate [4]. We describe a significant reduction in two groups of microbiota that help in maintaining the integrity of the large intestinal mucosa. Quoting Vollaard's and Donskey's work, Zandstra et al. agree that SDD is a contradiction in terms. We apparently disagree in our concern that SDD might have a "dark side", i.e. that some important beneficial microbiota are harmed by SDD. Besides, there is additional collateral damage: in the analysis of point-prevalence cultures from the de Smet study [6], an increase of intestinal colonisation by resistant organisms was observed after cessation of SDD [7].

None of the articles cited by Zandstra et al. describe the use of molecular methods for detection and/or enumeration of the intestinal microbiota. Bacteria from the *F. prausnitzii* group are highly sensitive to oxygen and require very specific growth media. Culture-based quantification yields a high degree of culture bias. These limitations of culture-based microbiological techniques have precluded reliable testing of the effects of antibiotics (i.e. SDD) on the intestinal microbiota. We are obviously not the first to claim that SDD is not selective. We are, however, the first to back up these claims using absolute numbers of faecal bacteria derived from a quantitatively reliable, molecular method.

Referring to Wensinck as an argument that not *F. prausnitzii* but clostridia contribute to colonisation resistance (CR), Zandstra et al. display a misunderstanding of the composition of the intestinal microbiota. Although phenotypically Gram-negative, *F. prausnitzii* are genetically closely related to the Gram-positive clostridia Zandstra et al. refer to. In fact, they belong to clostridial cluster IV [8]. These phylogenetic relations have only been discovered since the dawn of the molecular era.

We agree that the clinical impact of *F. prausnitzii* reduction in the critically ill is unclear—at least, that this should be further studied; we do not know whether there is a critical threshold of butyrate substrate for colonocytes to survive, or to maintain the integrity of the large intestinal mucosa. Recent studies have shown an anti-inflammatory effect of *F. prausnitzii* in Crohn's disease that could also be beneficial for the critically ill [9]. We have, however, provided novel information that may explain the discrepancy of effective reduction of *Enterobacteriaceae* by SDD, which fails to translate into further survival benefit in comparison with selective oropharyngeal decontamination (SOD).

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R. F. Benus · H. J. Harmsen · T. S. van der Werf (✉)
University Medical Center Groningen, Internal Medicine, Hanzeplein 1, P.O. Box 30001, 9700 RB Groningen, The Netherlands
e-mail: t.s.van.der.werf@int.umcg.nl
Tel.: +31-50-3611501
Fax: +31-50-3613216